A monoclonal anti-SARS-COV-2 IgG administered by intravenous or nebulization route reduces viral load in upper and lower respiratory tract

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Introduction:

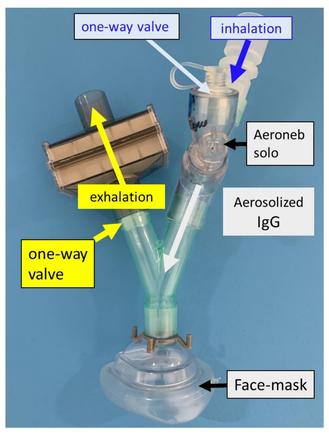
The SARS-CoV-2 pandemic has affected more than 526 million people worldwide resulting until early 2022 in over 6 million deaths. Vaccination remains the best solution to protect populations by allowing an effective humoral response. However, a part of the population, essentially immunocompromised individuals, can still develop severe forms of the disease due to a reduced capacity to respond to infection and vaccines. Icosagen developed an immunoglobulin G (IgG) (VH16VL104 IgG) with neutralising efficacy against the spike protein of most variants of concern. Here we show the efficacy of Icosagen antibody administered by aerosol or intravenous route in non human primates (NHP), 24h after exposure to a high dose of SARS-CoV-2.

Objectives: Optimization of inhalation IgG treatment & Evaluation *in vivo* of the neutralising efficacy of an IgG in a preclinical model of COVID19

1/ VH16VL104 IgG nebulization development adapted to anesthetized macaques
2/ Inhalation or intravenous treatment : pharmacokinetic and biodistribution of VH16VL104 IgG
3/ Efficacy study 24 hours after cynomolgus macaques nasal and Intra-tracheal exposure to high dose of SARS-COV-2 *delta strain*

Nebulization protocol validation :

Mesh Nebulization protocol :
Spontaneous ventilation
Anesthetized animals
Target : URT and LRT

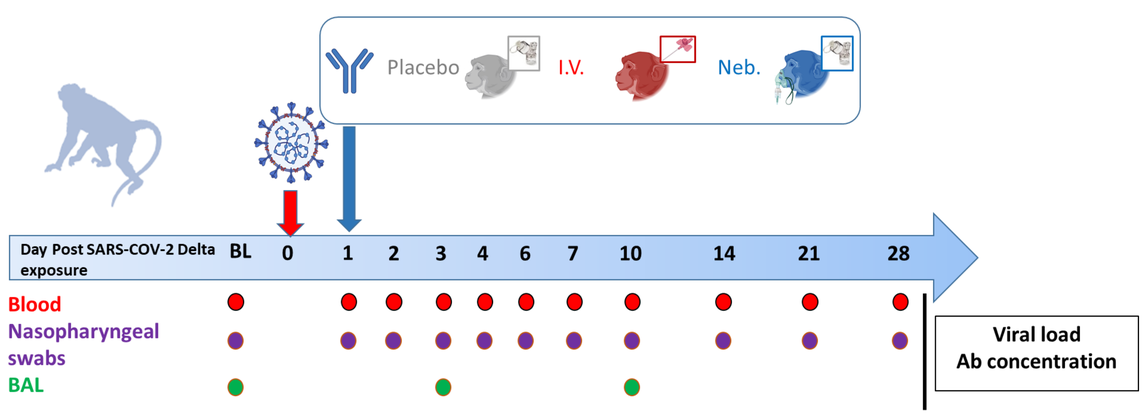


PET-scan imaging :
[18]-FDG nebulization to optimize inhalation protocol and prototype

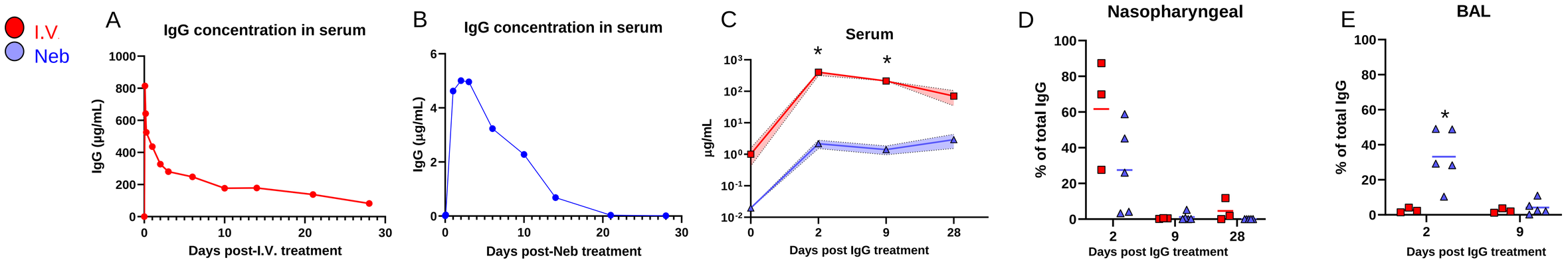
Respiratory tract deposition pattern of 40 MBq of 18-FDG nebulized with vibrating mesh nebulization prototype in NHP. Three cynomolgus macaques anesthetized and in spontaneous breathing were exposed by inhalation to [18]-FDG to validate the procedure and the total respiratory tract targeting.
Fraction of initial radioactivity deposited : **33.95% total respiratory tract. Average distribution: 20.26% URT and 9.47% LRT**

Preclinical efficacy study against SARS-COV-2 *delta strain*:

Study design: SARS-CoV-2 exposure (10^5 $TCID_{50}$ Delta strain) : combined intranasal and intratracheal routes
VH16VL104 treatment at 25mg.kg-1 24 hours after challenge : intravenously (in red) or by inhalation (in blue) Control group including historical controls is in grey
Follow-up on blood, nasopharyngeal swabs and BAL : monoclonal IgG concentrations and viral load



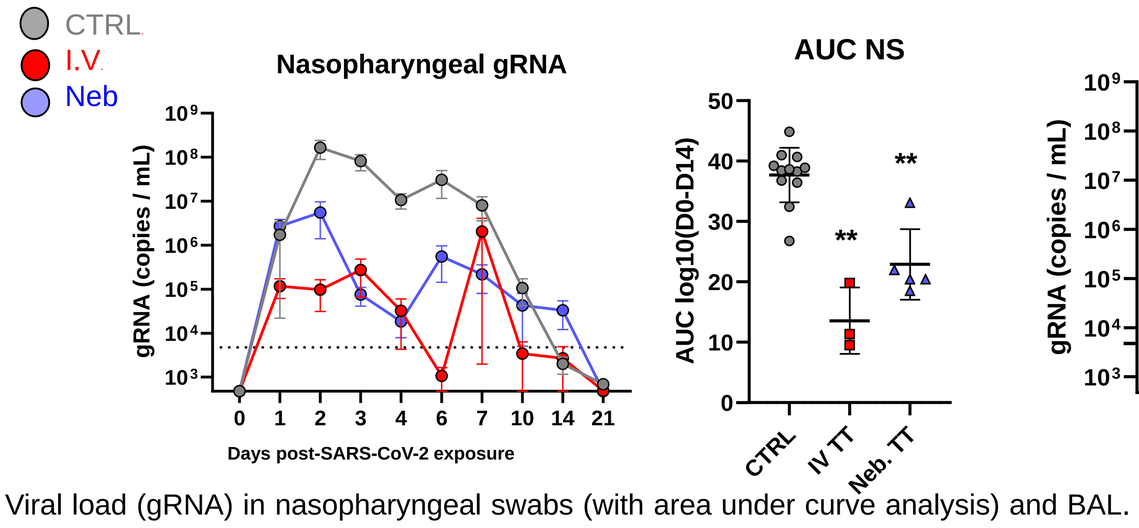
Pharmacokinetic and biodistribution of VH16VL104 :



Figures A & B: VH16VL104 concentration in serum after single dose administration (25mg.kg^{-1}) : IV route in red and Neb in blue (one NHP per treatment)
Figures C, D & E: Systemic, Upper and Lower Respiratory tract monoclonal IgG concentration after IV or Nebulization treatment (25mg.kg^{-1}) 24h post SARS-CoV-2 exposure
VH16VL104 concentration in µg/mL in serum and in percentage of total IgG in Broncho-alveolar lavages (BAL) and nasopharyngeal swabs
Mann-Whitney unpaired two-tailed t-test, *p* values: * < 0.05.

VH16VL104 concentration in BAL Day 2 post-treatment: **33.0% +/-SD(16.2) of the total IgG post-nebulization**
2.6% +/-SD(1.4) of the total IgG post-intravenous

Neb route results in a 10-fold higher pulmonary concentration 2 days post-treatment
I.V. route results in a 100-fold higher systemic concentration during 28 days



Reduction of Viral Load at day 3 post-exposure (Median) :
Nasopharyngeal swabs :
2.5 Log_{10} IV route
2.8 Log_{10} Neb route
BAL :
1.8 Log_{10} IV route
1.8 Log_{10} Neb route

Viral load (gRNA) in nasopharyngeal swabs (with area under curve analysis) and BAL. Mann-Whitney unpaired two-tailed t-test, p values: ** < 0.01. The dotted line represents the limit of quantification

Conclusions :

Vibrating Mesh Nebulization can efficiently administer monoclonal antibodies in the respiratory tract. Nebulization can exert immediate strong antiviral activity by delivering high concentration of treatment in the lung. VH16VL104 shows efficacy against SARS-CoV-2 and persistence in a preclinical model of COVID19.

Nebulization route of administration may be of interest against other respiratory pathogens when a rapid and very concentrated therapeutic pulmonary bolus is crucial.